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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,819	11/03/2006	David S. Garvey	102258.174 US3	7604
25270 7590 05/05/2009 WILMERHALE/NITROMED 1875 PENNSYLVANIA AVE, NW WASHINGTON, DC 20006			EXAMINER CHUNG, SUSANNAH LEE	
			ART UNIT	PAPER NUMBER
			1626	
			NOTIFICATION DATE	DELIVERY MODE
			05/05/2009	ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

teresa.carvalho@wilmerhale.com  
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deborah.lee@wilmerhale.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/568,819	<b>Applicant(s)</b> GARVEY ET AL.	
	<b>Examiner</b> SUSANNAH CHUNG	<b>Art Unit</b> 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 15 April 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-25 is/are pending in the application.
- 4a) Of the above claim(s) 4,5,7-12 and 18-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,6 and 13-17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9/21/07</u> .   | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

Claims 1-25 are pending in the instant application.

#### ***Priority***

This application is a 371 of PCT/US04/26910, filed 08/20/2004, which claims benefit of 60/498,309, filed 08/28/2003, and claims benefit of 60/535,542, filed 01/12/2004.

#### ***Information Disclosure Statement***

The information disclosure statement (IDS), filed on 9/21/2007 has been considered. Please refer to Applicant's copy of the 1449 submitted herewith.

#### ***Response to Election/Restrictions***

Applicant's election with traverse of Group I, compound claims 1-6 and 13-17, in the reply filed on 4/15/2009 is acknowledged. Also, the election of 2,2-bis(nitroxy)propyl-2-(N-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)pentanamido)-3-methylbutanoate for search and examination purposes is acknowledged. Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement so the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore, for the above reasons, the requirement is still deemed proper and is therefore maintained.

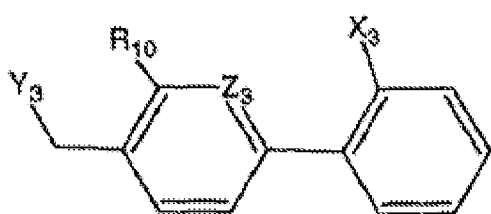
#### ***Scope of the Elected Invention***

Claims 1-25 are pending in this application. Claims 4-5, 7-12, and 18-25 are withdrawn from further consideration by the examiner, 37 C.F.R. §1.142(b), as being drawn to a non-elected invention. The withdrawn subject matter is patentably distinct

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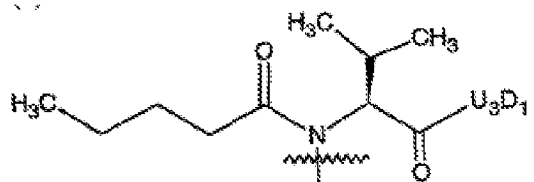
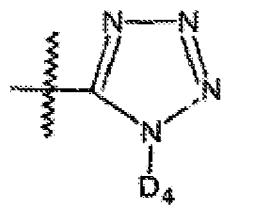
from the elected subject matter as it differs in structure and element and would require separate search considerations. In addition, a reference, which anticipates one group, would not render obvious the other.

The scope of the elected subject matter that will be examined and searched is as follows: Claims 1-3, 6 and 13-17 drawn to compounds of formula (I),



, depicted in claim 1, page 94, wherein:

**X3** is a tetrazole moiety of formula (1),



**Y3** is a carboxamide moiety of formula (2),

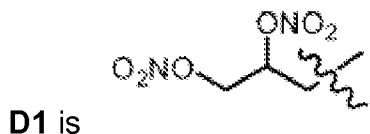
**Z3** is  $-\text{CH}-$ ;

**R10** is H;

**D4** is H;

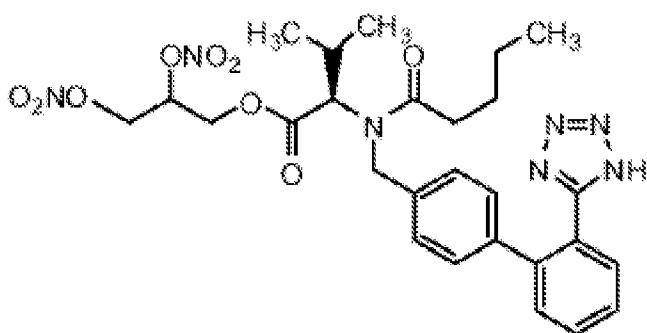
**U3** is O; and

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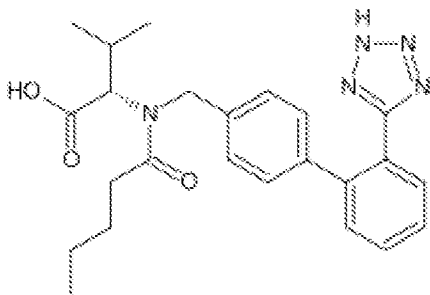
### ***Summary of the Elected Invention***

The instant invention is drawn to nitrosated or nitrosylated compounds. In particular, Applicants have elected the compound 2,2-bis(nitroso)propyl-2-(N-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)pentanamido)-3-methylbutanoate,



, for search and examination purposes.

This compound is also known as nitrosated or nitrosylated valsartan. Valsartan is (2S)-3-methyl-2-[N-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)pentanamido]-



butanoic acid,

. The difference between the instantly

claimed invention and the known valsartan compound is that the instantly claimed compound is nitrosated or nitrosylated at the instant D1 position. Claims 1-3, 6 and 13-17 read on the instantly elected species.

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***Claim Rejections - 35 USC § 112, 2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims must stand alone to define the invention and incorporation into claims by express reference to the specification is not permitted. Ex parte Fressola, 27 USPQ 2d 1608. Claims that require one to read the specification to determine the metes and bounds of the invention are repugnant to modern practice in the Office and are properly rejected under 35 USC 112, 2<sup>nd</sup> paragraph, as failing to particularly point out and distinctly claim the invention. Id. At 1609. Specifically, claim 3 claims a list of nitrosated or nitrosylated compounds using the ACS registry numbers (i.e. 124750-92-1) and other shorthand to describe the compounds (i.e. SR-47436). This requires one to read into the specification to determine the metes and bounds of the claim. Therefore, claim 3 is rejected as indefinite and appropriate correction is required.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

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only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 6 and 13-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Loscalzo, et al (U.S. Pat. No. 6,635,273B1, filed October 27, 2000). In claim 29, found in column 22, the method of using a nitrosated angiotensin II receptor antagonist is claimed. In column 6, starting approximately line 61, the definition of angiotensin II receptor antagonist is defined as valsartan. Therefore when the claims are given its broadest reasonable interpretation, the instantly claimed nitrosated or nitrosylated valsartan compound was claimed and taught in U.S. Pat. No. 6,635,273.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

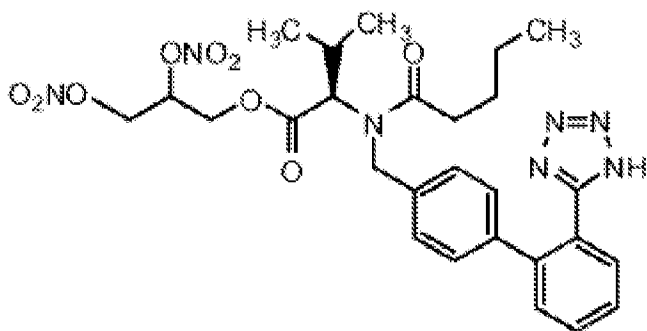
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The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 6 and 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buhlmayer et al., US Pat No. 5,399,578, published March 21, 1995 in view of Loscalzo, et al, U.S. Pat. No. 6,635,273B1, filed October 27, 2000.

The instant invention is drawn to nitrosated or nitrosylated compounds. In particular, Applicants have elected the compound 2,2-bis(nitroso)propyl-2-(N-((2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl)pentanamido)-3-methylbutanoate,



, for search and examination purposes.

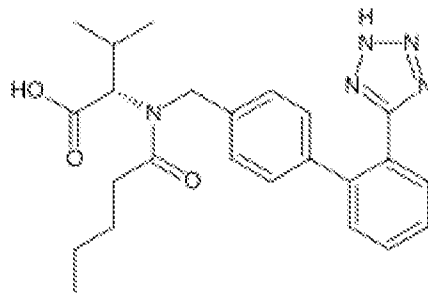
This compound is also known as nitrosated or nitrosylated valsartan.

Determination of the scope and content of the prior art (MPEP § 2141.01)

Buhlmayer teaches how to make and use valsartan. See US Pat No 5,399,578, claims 1-7, column 64. Valsartan is (2S)-3-methyl-2-[N-({4-[2-(2H-1,2,3,4-tetrazol-5-



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yl)phenyl]phenyl)methyl)pentanamido]-butanoic acid,

Valsartan is an angiotensin II receptor antagonist (more commonly called an "ARB", which stands for Angiotensin Receptor Blocker), acting on the AT1 subtype. In the U.S., valsartan is indicated for treatment of high blood pressure, of congestive heart failure (CHF), and post-myocardial infarction (MI). It is marketed by Novartis under the trade name Diovan. In 2005, Diovan was prescribed more than 12 million times in the United States and global sales were approximately \$6 billion.

Loscalzo teaches a method of using a nitrosated angiotensin II receptor antagonist is claimed. In column 6, starting approximately line 61, the definition of angiotensin II receptor antagonist is defined as valsartan. Therefore, nitrosated valsartan was claimed and taught in U.S. Pat. No. 6,635,273. Also see U.S. Pat. No. 6,635,273B1, filed October 27, 2000, claim 29, column 22.

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The difference between the instantly claimed invention and the known valsartan compound is that the instantly claimed compound is nitrosated or nitrosylated at the instant D1 position with various NO or NO<sub>2</sub> groups. It is noted that the instant claims generically claims a NO or NO<sub>2</sub> group at the D1 position. It encompasses a variety of different compounds as long as there is a NO or NO<sub>2</sub> moiety in the group.

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*Finding of prima facie obviousness – rationale and motivation (MPEP § 2142-2413)*

However, in the absence of showing unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention when faced with Buhlmayer and Loscalzo that valsartan can be nitrosated or nitrosylated. Although Loscalzo and Buhlmayer are silent as to the nitro moiety at the D1 position, it would be obvious to a skilled artisan to add various nitro moieties at that position.

The claims will be given its broadest reasonable interpretation. The instant invention is drawn to nitrosated or nitrosylated compounds. These terms are understood by a skilled artisan to mean any compound containing a NO or NO<sub>2</sub> group.

Nitrosated or nitrosylated compounds are well known in the art. For example, Garvey et al. teaches how to make and use nitrosated or nitrosylated taxane compounds. See US Pat No 6,656,966 B2, claims, especially claims 33-35, column 60, wherein various nitro groups are described. Garvey teaches how to make various nitro moieties off the taxane compound. See column 30, approximately lines 17-47, wherein the term “nitric oxide” is further defined as encompassing any nitrogen monoxide releasing, delivering, or transferring compounds. Garvey also teaches that nitrosated and nitrosylated compounds have additional therapeutic effects to specific patient populations such as the elderly, wherein the compounds will reduce side effects in patients affected by oxidative stress and/or endothelial dysfunctions.

Guided by the teaching of Buhlmayer and Loscalzo one skilled in the art would be able to make the instantly claimed nitrosated or nitrosylated valsartan compounds.

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The motivation would be to prepare similar compounds that are pharmacologically active to treat cardiovascular disorders.

The instant obviousness rejection is based on the close structural similarity of the instantly claimed compounds to the prior art compounds and the common utility shared among the compounds. There is an expectation among those of ordinary skill in the art that similar structural compounds will have similar properties and that modification of a known structure is mere experimentation within the means of a skilled artisan. See MPEP 2144.09(I). Optimization of a known compound is mere experimentation and is not patentable over the known compound. Therefore, claims 1-3, 6 and 13-17 are rejected as obvious over the prior art.

#### ***Telephone Inquiry***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Susannah Chung/  
Examiner, Art Unit 1626